



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

11/05/98

Food and Drug Administration  
Rockville MD 20867

Via Federal Express

NOV - 5 1998

**Warning Letter**

Thomas D. Brown, President  
Abbott Laboratories  
Diagnostics Division  
100 Abbott Park Road  
Abbott Park, Illinois 60064

Dear Mr. Brown:

During the period of July 6 through August 19, 1998, Mary K. Concannon and Chad E. Schmeier, Investigators from the Food and Drug Administration's (FDA) Chicago District Office; Jean Toth-Allen, Consumer Safety Officer, Center for Devices and Radiological Health (CDRH); and Charma Konnor, Director, Division of Bioresearch Monitoring, CDRH visited Abbott Laboratories' Diagnostics Division. The purpose of their visit was to conduct an inspection to determine whether your activities as a sponsor/monitor of an investigational study of [REDACTED] complied with applicable FDA regulations. The inspection was expanded to include review of activities of the investigational studies of [REDACTED]

[REDACTED] All three of these products are in-vitro diagnostics (IVDs). IVDs are devices as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notifications [510(k)] are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Review of the inspectional report submitted by the district revealed that serious deviations were noted during the inspection. These deviations were listed on form FDA-483, "Inspectional Observations," which was presented to and discussed with Robert C. Doss, Ph.D., Vice President of Quality Assurance/Regulatory Affairs, Diagnostics Division, at the conclusion of the inspection.

We acknowledge receipt of a response from Dr. Doss, dated August 27, 1998, and addressed to Mr. Robert Fish. This response and attached cover letter addressed each of the form FDA-483 items and included a Commitment Schedule summarizing the planned corrective actions and their proposed completion dates. In the cover letter, Dr. Doss expressed concern with the fact that the FDA investigators stated

that some of their expectations were based in part on 21 CFR Part 812. He noted that, as a result of the nature of the testing involved, the IVDs in question are exempt from Part 812. If IVDs meet the requirements of 21 CFR 812.2(c)(3), they are exempt from Part 812. However, that exemption does not preclude the need for valid scientific data from a properly conducted clinical investigation in support of a PMA submission. FDA's interpretation of the meaning of the abbreviated requirements and exemptions addressed in 21 CFR 812.2 was recently discussed in the preamble to the final rule for clinical investigator disqualification (62 Federal Register (FR) 12087, March 14, 1997) (copy enclosed). It reads:

The exemptions and abbreviated requirements described in part 812 for certain investigations are intended to relate to those procedures and requirements under part 812 associated with submitting an IDE application or obtaining an IDE prior to conducting an investigation. Section 812.2 is not intended to eliminate the responsibility of clinical investigators of devices to abide by procedures and standards associated with good scientific practice. Whether or not an investigation requires an IDE, every clinical investigator whose work may be considered in connection with a marketing application is expected to comply with the agency's regulations and scientific standards relating to informed consent, IRB oversight, inspection, adherence to investigational protocols, and pertinent report and recordkeeping (62 FR 12088 –12089).

These expectations with regard to clinical studies extend to the sponsors of such studies as well.

Moreover, Abbott submitted PMAs that include data collected during investigational studies. PMA submissions are subject to the regulations in 21 CFR 814 – Premarket Approval of Medical Devices. 21 CFR 814.45(c) states that FDA will use the criteria specified in 21 CFR 860.7 to determine the safety and effectiveness of a device in deciding whether to approve or deny approval of a PMA. According to 21 CFR 860.7(c)(1), in an attempt to substantiate the safety and effectiveness of a device, FDA relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. Further, 21 CFR 860.7(g)(1) states that it is the responsibility of each manufacturer to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the FDA. Although IVDs meeting the requirements of 21 CFR 812.2(c)(3) are exempt from the specific provisions of Part 812, review of those provisions will provide a general idea of what FDA considers to be guiding principles regarding the conduct of clinical investigations and the protection of subjects.

With regard to the issues addressed in the form FDA-483 pertaining to the present PMA submissions, Dr. Doss responded that Abbott has or will submit all protocols used during the studies that were not included in the original PMA submissions.

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**Moreover, specific data will be reanalyzed and submitted. However, none of these actions provide assurance that the data submitted in support of these PMAs are accurate and complete. Evidence collected during the inspection revealed minimal monitoring, a lack of study close-out data audits, and a lack of data verification forms from the clinical investigational sites. FDA has received a copy of the amendment Abbott has submitted in response to an August 31 letter from FDA placing a hold on review of the PMA for [REDACTED]. We also acknowledge receipt of an October 23 letter addressed to Dr. Carl T. DeMarco which states that Abbott has retained [REDACTED] as of October 20 to provide a third party audit of the three PMA applications referred to above. Please send a copy of the audit plan draft to the Division of Bioresearch Monitoring (DBM) for review. This should be sent to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Robert Fish.**

**When responding to the form FDA-483 item regarding Abbott's investigational use only (IUO) certification procedure, Dr. Doss referred to the draft version of the FDA Compliance Policy Guide (CPG) covering the commercialization of investigational use IVD devices. The draft CPG, dated January 5, 1998, is titled "Commercialization of In Vitro Diagnostic Devices (IVD's) Labeled for Research Use Only or Investigational Use Only" (copy enclosed). FDA developed this CPG partly as a means of addressing the fact that a number of IVDs presently in commercial distribution lack both approval and clearance. Moreover, it serves as a guide for IVD manufacturers presently in the development stage with new products.**

**The certification program discussed within this CPG offers a guide by which sponsors could document that the data presented to support their submissions were collected in a scientifically valid manner. Appendix C describes the certification program. The items listed here are similar to the statements expected to appear in investigator agreements for premarket clinical investigations. This CPG presents a remedial program to assist sponsors in bringing IVDs that are improperly marketed into compliance with FDA regulations and a guide for IVD manufacturers regarding FDA expectations prior to marketing.**

**The inspectional report contains a copy of Abbott's draft procedure titled "Procedure and Documentation for Certification of Investigators and/or Researchers Using Abbott Investigational Use Only (IUO) Products." Part A of this draft procedure "For Investigational Purposes Only," contains what would be expected in a protocol-controlled investigational study. However, Part B of this draft procedure, "Independent Investigator/Researcher Sponsored Studies," proposes to allow clinical investigators access to investigational IVDs for research purposes, with each individual investigator free to develop their own study protocol(s). This would make it difficult or impossible to combine resulting data in a submission for marketing**

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**approval or clearance. As stated in Appendix C of the draft CPG referenced above, "...the IVD will be used only for the purpose of gathering data to support appropriate submission to the FDA, and will not be used for diagnostic purposes without confirmation by another medically established diagnostic device or procedure."**

**The inspectional report includes information that investigators presently in Abbott's certification program for [REDACTED] have a choice to follow any or all of five different sections of a protocol supplied by Abbott. They may also supply their own protocol. Moreover, Ms. Virginia Schaefer, Clinical Research Associate who is responsible for the [REDACTED] clinical studies, is quoted as stating that the IUO certification program is distinct from actual clinical studies. The inspectional report also provides evidence that requirements of the certification program used for [REDACTED] specifically quarterly reporting and actions to be taken if reports are not forthcoming, have not been followed. Part B of the certification program as presently drafted by Abbott, and the program as presently in effect for [REDACTED], are not appropriate means for studying investigational devices. Moreover, the decision as to whether the data received from the investigators of [REDACTED] under the present certification program is relevant to the submitted PMA should be made by the appropriate personnel in the Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH).**

**In the Commitment Schedule included with Dr. Doss' response, five different work instructions are proposed for approval or revision as corrective actions for a number of the deficiencies noted. We acknowledge receipt of an updated version of this schedule that includes completion dates, in a facsimile addressed to Mr. Carl DeMarco and Drs. Peter Maxim and Pat Reeves on October 5. Please forward a copy of each of the five completed work instructions to the address given above.**

**Sponsors are responsible for ensuring that all clinical investigations are conducted in accordance with the signed investigator agreements, the investigational plan, and the applicable FDA regulations for protecting the right, safety, and welfare of the subjects included in the study. Moreover, it is the responsibility of the sponsor to assure that adequate, valid scientific evidence exists and to supply such evidence to FDA to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use.**

**Within fifteen (15) working days of receipt of this letter, please provide this office with written documentation of any other specific steps you have taken or will be taking to correct these violations and to prevent the recurrence of similar violations in current and future studies. We want you to be aware that failure to comply with the law may result in further regulatory action against you or the device by FDA without further notice. These actions include, but are not limited to, seizure, injunction, and civil money penalties.**

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A copy of this letter has been forwarded to our Chicago District Office, 300 South Riverside Plaza, Suite 550 South, Chicago, Illinois 60606. We request that a copy of your response be sent to that office.

If you have any questions or concerns, please contact Jean Toth-Allen or Robert Fish at (301) 594-4723.

Sincerely yours,



Lillian J. Gill  
Director  
Office of Compliance  
Center for Devices and Radiological  
Health

Enclosures

cc: Duane E. Burnham  
Chairman and Chief Executive Officer  
Abbott Laboratories

Robert C. Doss, Ph.D.  
Vice President of Quality Assurance/Regulatory Affairs  
Abbott Laboratories Diagnostic Division